CAS# 1746-01-6

Safety Data Sheet

2,3,7,8-Tetrachloro-dibenzo-p-dioxin

Division of Safety
National Institutes
of Health

WARNING!

THIS COMPOUND IS ACUTELY TOXIC IN SEVERAL MAMMALIAN SPECIES, CARCINOGENIC OR COCARCINOGENIC, TERATOGENIC, FETOTOXIC, AND POSSIBLY WEAKLY MUTAGENIC. IT IS READILY ABSORBED BY VARIOUS BODY TISSUES THROUGH THE SKIN AND RESPIRATORY AND INTESTINAL TRACTS AND TRANSPLACENTALLY. IT MAY IRRITATE TISSUES (SKIN, EYES, MUCOUS MEMBRANES, AND LUNGS) AND INDUCE SENSITIVITY. AVOID FORMATION AND BREATHING OF AEROSOLS.

LABORATORY OPERATIONS SHOULD BE CONDUCTED IN A FUME HOOD, GLOVE BOX, OR VENTILATED CABINET.

AVOID SKIN CONTACT: IF EXPOSED, WASH WITH SOAP AND COLD WATER. AVOID WASHING WITH SOLVENTS AND EXPOSURE TO UV LIGHT. AVOID RUBBING OF SKIN OR INCREASING ITS TEMPERATURE.

FOR EYE EXPOSURE, IRRIGATE IMMEDIATELY WITH LARGE AMOUNTS OF WATER. FOR INGESTION, INDUCE VOMITING. DRINK MILK OR WATER. REFER FOR GASTRIC LAVAGE. FOR INHALATION, REMOVE VICTIM PROMPTLY TO CLEAN AIR. ADMINISTER RESCUE BREATHING IF NECESSARY. REFER TO PHYSICIAN.

IN CASE OF LABORATORY SPILL, WEAR PROTECTIVE CLOTHING DURING CLEANUP. AVOID SKIN CONTACT OR BREATHING OF AEROSOLS. USE ACETONE TO DISSOLVE COMPOUND. USE ABSORBENT PAPER TO MOP UP SPILL. WASH DOWN AREA WITH CHLOROTHENE NU FOLLOWED BY SOAP AND WATER. DISPOSE OF WASTE SOLUTIONS AND MATERIALS APPROPRIATELY.

Issued: 1/89

Prepared by the Environmental Control and Research Program

A. Background

2,3,7,8-Tetrachlorodibenzo-p-dioxin[A] (TCDD) is a colorless crystalline compound. Its solubility in water is very low, that in fats, oils, and nonpolar solvents is higher.

TCDD has been described as "... one of the most perplexing and potentially dangerous chemicals ever to pollute the environment. TCDD has been called the most toxic synthetic chemical known to man, although it has yet to be proven to claim a human victim" (American Academy of Clinical Toxicology, 1985). One reason for this is that the toxicity of TCDD varies by several orders of magnitude between animal species. It is highly teratogenic and fetotoxic in many species including the rhesus monkey but is at most only very weakly mutagenic. Its carcinogenicity is the subject of vigorous debate but the evidence is considered to be "sufficient" in animals and "inadequate" in man (IARC, 1982). TCDD is a contaminant in the manufacture of chlorophenol herbicides such as 2,4,5-T (2,4,5-trichlorophenoxyacetic acid), and epidemiological studies have been carried out on workers engaged in this manufacture as well as in the animal and human populations surrounding an explosion in a factory near Seveso, Italy. TCDD has also been implicated as the causative agent of various symptoms described by veterans exposed to this agent as a contaminant of the defoliant Agent Orange in Vietnam.

Most investigators do not assign permissible exposure limits in air to TCDD and advocate avoidance of all contact (e.g., Sittig, 1985). An 8-hr time-weighted average limit of 2 ng/m^3 has recently been considered appropriate, and one of 0.2 ng/m^3 has been recommended (Leung et al., 1988).

A vast number of monographs and reviews of the chemical, biological, and epidemiological properties of TCDD have been published in recent years. Among these are: IARC, 1977, 1982; Poland and Knutson, 1982; Tucker et al., 1983; Dioxin report, 1983; Poland and Kimbrough, 1984; Hutzinger et al., 1986.

B. Chemical and Physical Data

1. Chemical Abstract No.: 1746-01-6

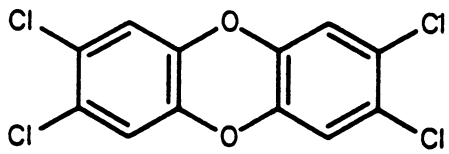
[A]The terms most commonly used as abbreviations for this compound, namely "TCDD" and "dioxin", are both chemically inaccurate. There exist 22 possible tetrachloro isomers, and altogether 75 chlorinated dibenzo-p-dioxins. Because of its widespread use, the synonym "TCDD" will be used in this Safety Data Sheet to refer to the 2,3,7,8-tetrachloro isomer. It should be noted that the name "Dioxin" has also been applied to dimethoxane, an entirely different type of compound (Windholz, 1983). This use is now obsolete.

2. Synonyms:

TCDBD; 2,3,7,8-tetrachlorodibenzo-1,4-dioxin, Dioxin, Dibenzo[b,e][1,4]dioxin, 2,3,7,8-tetrachloro - (9CI).

3. Molecular formula: $C_{12}H_4Cl_4O_2$

structure:



4. Density: 1.827 g/ml for solid at 25°C (Schroy et al., 1985).

5. Absorption spectroscopy: UV: λ_{max} (log ε) 230 (3.75), 248 (3.47) and 307 (Pohland and Yang, 1972; Crosby et al., 1971). Infrared and phosphorescence spectra and mass spectral data have been reported (Pohland and Yang, 1972; Chen, 1973).

6. Volatility: Low (3.46×10^{-9} mm Hg at 30.1°C) (Schroy et al., 1985).

7. Solubility: Very low in water (3.17×10^{-7} g/L at 25°C); solubilities (in g/l) in: chlorobenzene (0.72), benzene (0.57), acetone (0.11), chloroform (0.37), fats, and oils. Preparation for oral or parenteral administration is usually an acetone solution diluted with corn oil.

8. Description: Colorless needles.

9. Boiling point: 521.2°C.

Melting point: 305°C.

10. Stability: Solid TCDD is very stable at room temperature and at somewhat elevated temperatures. Decomposition begins at 500°C and is virtually complete in 21 sec at 800°C (Sittig, 1985). Pure TCDD, in bulk or on glass plates, is stable to ultraviolet light but is rapidly decomposed in methanol or ethanol solution. In formulations with herbicides, TCDD rapidly decomposes on exposure to ultraviolet irradiation (including sunlight) (Crosby et al., 1971; Crosby and Wong, 1977). The reaction is a gradual dechlorination to less toxic benzodioxins.

11. Chemical reactivity: TCDD decomposes (cleavage of the ether linkages) in the dark by micellar catalysis with chloroiodides of cationic detergents (Botré et al., 1979) and by ruthenium tetroxide (half time at 20°C, 600 min; at 70°C, less than 15 min) (Ayres, 1981).

12. Flash point: No data.

13. Autoignition temperature: No data.

14. Explosive limits in air: No data.

Fire, Explosion, and Reactivity Hazard Data

There are no specific directives for TCDD; there appear to be no explosion or reactivity hazards, and fire would, if anything, decompose TCDD to less toxic materials. The information below is designed to protect fire fighters and laboratory personnel from the highly toxic effects of undecomposed TCDD.

1. In case of fire, all laboratory personnel not engaged in fire fighting should immediately leave the affected area, remove all clothing, and scrub vigorously all potentially exposed areas with mild soap and water (whether or not they have been so exposed). Fire-fighting personnel should wear complete protective clothing with air-supplied respirators. Dry chemical fire extinguishers should be used. Dust formation should be avoided.

2. Exposure of significant amounts of TCDD to high temperatures may result in the liberation of chlorine and/or hydrochloric acid (this has not been demonstrated experimentally).

3. Conditions contributing to instability include exposure to heat and ultraviolet light (in the presence of solvents).

4. Incompatible with very strong oxidizing agents.

5. Nonspark equipment is not required.

Operational Procedures

For detailed recommendations on the safe handling of TCDD in the laboratory see Taft et al., 1983 and Futrell, 1983. All operations and equipment should be strictly segregated.

The NIH Guidelines for the Laboratory Use of Chemical Carcinogens describe operational practices to be followed when potentially carcinogenic chemicals are used in NIH laboratories. The NIH Guidelines should be consulted to identify the proper use conditions required and specific controls to be implemented during normal and complex operations or manipulations involving TCDD.

It should be emphasized that this data sheet and the NIH Guidelines are intended as starting points for the implementation of good laboratory practices when using this compound. The practices and procedures described in the following sections pertain to the National Institutes of Health and may not be universally applicable to other institutions. Administrators and/or researchers at other institutions should modify the following items as needed to reflect their individual management system and current occupational and environmental regulations.

1. Chemical inactivation: No validated method reported.

2. Decontamination: Turn off equipment that could be affected by TCDD or the materials used for cleanup. If there is any uncertainty regarding the procedures to be followed for decontamination, call the NIH Fire Department (dial 116) for assistance. Use absorbent paper to mop up spill. Wipe off surfaces with Chlorothene Nu solvent (Dow), followed by detergent and water. Glassware should be rinsed in a hood with detergent, followed by soap and water. Animal cages should be washed with water.

3. Disposal: No waste streams containing TCDD shall be disposed of in sinks or general refuse. Surplus TCDD or chemical waste streams contaminated with TCDD shall be handled as hazardous chemical waste and disposed of in accordance with the NIH chemical waste disposal system. Nonchemical waste (e.g., animal carcasses and bedding) containing TCDD shall be handled and packaged for incineration in accordance with the NIH medical-pathological waste disposal system. Potentially infectious waste (e.g., tissue cultures) containing TCDD shall be disinfected by heat using a standard autoclave treatment and packaged for incineration, as above. Burnable waste (e.g., absorbent bench top liners) minimally contaminated with TCDD shall be handled as potentially infectious waste and packaged for incineration, as above. Absorbent materials (e.g., associated with spill cleanup) grossly contaminated shall be handled in accordance with the chemical waste disposal system. Radioactive waste containing TCDD shall be handled in accordance with the NIH radioactive waste disposal system. All incinerations should be carried out at 1,000°C or above (Esposito et al., 1982).

4. Storage: Store solid TCDD in a limited access area in sealed ampoules or in bottles with caps with polyethylene cone liners inside a sealed secondary container. These should be kept in a solvent storage cabinet, deep freeze, or explosion-safe refrigerator. Avoid exposure to light and moisture. Store working quantities of TCDD and its solutions in an explosion-safe refrigerator in the work area in the dark.

Monitoring and Measurement Procedures Including Direct Field Measurements and Sampling for Subsequent Laboratory Analysis

1. Sampling and sample preparation: The most generally used procedures for biological and environmental sample preparation are based on the original procedures by Baughman and Meselson (1973) which consist of digestion with alkali, extraction with hexane, further cleanup on an alumina column, and re-extraction. Later methods are mostly refinements of this procedure (Shadoff and Hummel, 1978; Thomas et al., 1980) and have been summarized

(Crummett, 1983). More specific methods of sample preparation have been described for tissue samples (Gross, 1982) and for air filter material (Harvan et al., 1981).

2. Analysis: The most commonly used method for TCDD analysis after initial cleanup is gas chromatography-mass spectrometry (GC-MS) because of the high sensitivity (0.1 - 1 ppt) required. Low resolution MS may be used for initial screening, whereas high resolution MS is reserved for those cases where higher limits of sensitivity are required (Shadoff and Hummel, 1978; Harvan et al., 1981). Separation of tetrachlorodibenzo-p-dioxins from each other is accomplished by means of capillary gas chromatography/atmospheric pressure negative chemical ionization-MS (Mitchum et al., 1982; Korfmacher et al., 1984). Other methods in use include MS/MS and Fourier transform MS (discussed by Gross, 1982). A proposed biological method with required sensitivity but lower specificity is based on induction of aryl hydrocarbon hydroxylase activity (Albro et al., 1979).

Biological Effects (Animal and Human)

Note: Information pertaining to 1, 2, and 3 below has been reviewed (Neal et al., 1982; Gasiewicz et al., 1983).

1. Absorption: TCDD is absorbed and produces toxic effects via the oral and parenteral routes and through the skin. It is also transmitted through the placenta.

2. Distribution and pharmacokinetics: In most species the largest amount of parenterally administered TCDD is retained in liver and adipose tissue for some time; in the monkey almost all is found in muscle and skin, virtually all in unmetabolized form. In man, a single oral dose of labeled TCDD results in over 87% absorption from the intestine, distribution to adipose tissue, and fecal excretion with a half time of about 2,000 days. During the first week approximately 13% of the radioactivity administered is excreted, with very slow subsequent excretion. There is no measurable urinary excretion (Poiger and Schlatter, 1986). At the subcellular level, considerable amounts of TCDD are found in the hepatic microsomal fraction in rodents.

3. Metabolism and excretion: It used to be believed that TCDD undergoes little or no metabolic transformation in the animal body; in recent years, however, considerable metabolism has been demonstrated, but since metabolites have not been found to be accumulated in tissues it must be assumed that, once formed, the metabolites are rapidly excreted. Metabolic studies have been carried out in the hamster (Olson et al., 1980), rat (Ramsey et al., 1982), mouse (Koshakji et al., 1984), guinea pig (Olson, 1986), and dog (Poiger and Buser, 1983). The extent of metabolism is highly species-dependent, and the cited articles should be consulted for details; for instance, the guinea pig appears not to excrete metabolites efficiently. As a generalized statement it appears that metabolism (to whatever extent)

consists of gradual oxidative dechlorination and opening of one or both ether linkages. (A tentative metabolic scheme has been depicted (Poiger et al., 1982).) The process appears to be one of detoxification since all metabolites so far identified exhibit toxicities at least 100 times less (in the guinea pig) than does TCDD. Metabolites are excreted in either free form or as glucuronides. As mentioned before, excretion occurs in most species via the feces but in hamster and mice in the urine.

The mechanism of toxicity (again highly species dependent) has been reviewed (Poland and Knutson, 1982; Vickers et al., 1985). According to this model (in analogy to the action of steroid hormones), TCDD enters the mammalian cell and binds with high affinity to the aromatic hydrocarbon receptor(s) in cytoplasm. This receptor has a low saturation capacity; as a result, the TCDD receptor complex translocates to the nucleus and binds to specific sites on cellular chromatin. TCDD is a potent inducer of several enzymes (microsomal mono-oxygenases, glucuronyltransferase, cytochrome P-450, etc. (Safe, 1983).

Toxic effects: The acute oral LD50 of TCDD varies greatly depending on animal species; in µg/kg the figures are as follows: guinea pig, 0.6-2; male rat, 22; female rat, 45; chicken, ca. 30; rhesus monkey, 70; dog, 20-200; rabbit, 115; mouse, 284; hamster, 1,160. The intraperitoneal LD50 is 60 for male rats, 25 for female rats, and over 3,000 for hamsters. The skin LD50 in rabbits is 275. Where humans fit into this range is not known, but acute toxicity in humans is probably not of great significance since no fatalities directly attributable to TCDD have been noted in any of the numerous industrial accidents.

Far more important are the long-term toxic effects of TCDD after sublethal doses; these also are largely species dependent. In the rabbit there is considerable degeneration of the liver and kidney, and death is believed to be due to liver toxicity; other species do not show as much liver involvement. Nearly all species show involution of lymphoid tissue and atrophy of the thymus and spleen. Several species, including man, develop porphyrin, which is probably related to a marked rise in the hepatic level of aminolevulinic acid synthetase (the rate-limiting enzyme in heme production) in experimental animals and in workers exposed to TCDD. On the skin, chloracne and hyperkeratosis are common findings in industrial accidents and have been reproduced in the rabbit, monkey, and hairless mouse. In the Seveso accident, chloracne lasted for 8-26 months (Reggiani, 1980). Monkeys fed a low level (500 ppt) of TCDD developed anemia, pancytopenia, and widespread hemorrhages; autopsy revealed hypertrophy of the epithelium of bronchi, bile duct, and pancreatic and salivary glands (Allen et al., 1977).

5. Carcinogenic effects: The relationship between TCDD exposure and carcinogenicity is not clear at this time, at least insofar as man is concerned (see extensive discussion in IARC, 1982). In particular, there is no report of human exposure to TCDD only, rather than to its admixture with herbicides and other contaminants of which TCDD represents a small percentage. Kociba et al. (1979), in a two-year chronic toxicity study in rats has described the appearance of a number of carcinomas but only at dose levels which produce severe toxic responses (reviewed by Hiremath et al., 1986). The general consensus appears to be that TCDD acts as a promoter of carcinogenicity for other carcinogens rather than as a direct inducer of tumors. Evidence for this view has been reviewed (Leung et al., 1988). It should also be noted that TCDD (in contrast with primary initiators of carcinogenesis) does not form covalent adducts with DNA in vitro or in vivo (Poland and Glover, 1979; Kociba and Schwetz, 1982) and shows little or no mutagenicity.

6. Mutagenic and teratogenic effects: The evidence for mutagenicity is conflicting but on balance indicates, at most, low mutagenicity in the Ames system (Geiger and Neal, 1981; IARC, 1982), with or without activating systems. On the other hand, TCDD is strongly fetotoxic in rats, mice, and rhesus monkeys (Allen et al., 1979; Smith et al., 1976; Giavini et al., 1982; McNulty, 1984).

Emergency Treatment (see Arena and Drew, 1986).

1. Skin and eye exposure: For skin exposure, remove contaminated clothing and wash skin with soap and water. Skin should not be rinsed with organic solvents or scanned with UV light. Since TCDD is readily absorbed through the skin, avoid rubbing of skin or increasing its temperature. For eye exposure, irrigate immediately with copious quantities of running water for at least 15 minutes. Obtain ophthalmological evaluation.

2. Ingestion: Drink plenty of water or milk. Induce vomiting. Refer for gastric lavage, followed by activated charcoal or saline cathartic.

3. Inhalation: Remove victim promptly to clean air. Administer rescue breathing if necessary.

4. Refer to physician at once. Consider treatment for pulmonary irritation.

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